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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 49/00, 51/06	A1	(11) International Publication Number: WO 96/00588 (43) International Publication Date: 11 January 1996 (11.01.96)
(21) International Application Number: PCT/GB95/01514 (22) International Filing Date: 28 June 1995 (28.06.95) (30) Priority Data: 08/266,835 28 June 1994 (28.06.94) US (71) Applicant (for all designated States except US): NYCOMED IMAGING A/S [NO/NO]; Nycoveien 1-2, N-0401 Oslo 4 (NO). (71) Applicant (for GB only): COCKBAIN, Julian, Roderick, Michaelson [GB/GB]; 27 Ladbroke Road, London W11 3PD (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): LADD, David, Lee [US/US]; Nycomed R+D Inc., 466 Devon Park Drive, P.O. Box 6630, Wayne, PA 19087-8630 (US). (74) Agents: COCKBAIN, Julian, R., M. et al.; Frank B. Dehn & Co., Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i>
(54) Title: LOW VISCOSITY CHELATING POLYMERS (57) Abstract Linear and cross-linked polymers suitable for use as agents for magnetic resonance imaging comprising units comprising the residue of a poly(amine) moiety linked to a chelating agent residue and to one or more pendant (poly)alkylene oxides.		

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LOW VISCOSITY CHELATING POLYMERS

5 This invention relates to chelating polymers useful as
magnetic resonance (MR) contrast agents for use in MR
imaging compositions and methods. More particularly,
this invention relates to linear and cross-linked α -
(polyamino)- ω -methoxy poly(alkyleneoxide)-DTPA polymers
10 and their metal chelates.

Magnetic resonance (MR) is widely used for obtaining
spatial images of human subjects for clinical diagnosis.
A review of this technology and clinical applications is
15 provided by D.P. Swanson et al., in Pharmaceuticals in
Medical Imaging, 1990, Macmillan Publishing Company,
pages 645-681.

MR images are derived as a composite of the effects of a
20 number of parameters which are analyzed and combined by
computer. Choice of the appropriate instrument
parameters, such as radio frequency (Rf), pulsing and
timing can be utilized to enhance or attenuate the
signals of any of the image-producing parameters thereby
25 improving image quality and provide better anatomical
and functional information. In many cases, MR imaging
has proven to be a valuable diagnostic tool, inasmuch as
normal and diseased tissue, by virtue of their
possessing different parameter values, can be
30 differentiated in the image.

In MR imaging, the in vivo image of an organ or tissue
is obtained by placing the body of a subject in a strong
external magnetic field, pulsing with radio frequency
35 energy, and observing the effect of the pulses on the
magnetic properties of the protons contained in and
surrounding the organ or tissue. A number of parameters

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can be measured. The proton relaxation times, T_1 and T_2 , are of primary importance. T_1 , also called the spin-lattice or longitudinal relaxation time, and T_2 , also called the spin-spin or transverse relaxation time, are functions of the chemical and physical environment of the organ or tissue water and are measured using Rf pulsing techniques. This information is analyzed as a function of spatial location by computer which transforms the information to generate an image.

10

Often the image produced lacks appropriate contrast, e.g., between normal and diseased tissue, reducing diagnostic effectiveness. To overcome this drawback, contrast agents have been used. Contrast agents are substances which exert an effect on the MR parameters of various chemical species proximal to them.

15

Theoretically, a contrast agent, if taken up preferentially by a certain portion of an organ or a certain type of tissue, e.g., diseased tissue, can provide contrast enhancement in the resultant images.

20

Inasmuch as MR images are strongly affected by variations in the T_1 and T_2 parameters, it is desirable to have a contrast agent which affects either or both parameters. Research has focused predominantly on two classes of magnetically active materials, i.e., paramagnetic materials, which act primarily to decrease T_1 , and superparamagnetic materials, which act primarily to decrease T_2 .

25

Paramagnetism occurs in materials that contain unpaired electrons. Paramagnetic materials are characterized by a weak magnetic susceptibility (response to an applied magnetic field). Paramagnetic materials become weakly magnetic in the presence of a magnetic field and rapidly lose such activity, i.e., demagnetize, once the external field has been removed. It has long been recognized that

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the addition of paramagnetic solutes to water causes a decrease in the T_1 parameter.

5 Paramagnetic materials, for example, Gd containing materials, have been used as MR contrast agents primarily because of their effect on T_1 . Gd has the largest number of unpaired electron (seven) in its 4f orbitals and exhibits the greatest longitudinal relaxivity of any element.

10

A major concern with the use of contrast agents for MR imaging is that many paramagnetic materials exert toxic effects on biological systems making them inappropriate for in vivo use. For example, the free solubilized form of Gd salts are quite toxic. To make the gadolinium ion more suitable for in vivo use, researchers have chelated it with diethylenetriaminepentaacetic acid (DTPA). A formulation of this material that has undergone extensive clinical testing consists of Gd-DTPA neutralized with two equivalents of N-methyl-D-glucamine (meglumine). This agent has been successful in enhancing human brain and renal tumors.

20

Despite its satisfactory relaxivity and safety, this formulation has several disadvantages. For example, due to its low molecular weight, Gd-DTPA dimeglumine is cleared very rapidly from the blood stream and tissue lesions (tumors). This limits the imaging window, the number of optimal images that can be taken after each injection, and increases the agents required dose and relative toxicity. In addition, the biodistribution of Gd-DTPA is suboptimal for imaging body tumors and infections due to its small molecular size.

Several approaches have been taken in attempts to overcome these disadvantages. For example, Gd and Gd-chelates have been chemically conjugated to macromolecular proteins such as albumin, polylysines and

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immunoglobulins. Drawbacks of conjugating DTPA to protein carriers for use in MR image enhancement include inappropriate biodistribution and toxicity. In addition, proteins provide a defined platform not subject to wide synthetic variation. Additionally, thermal sterilization of protein conjugates tends to be problematic, especially in the case of albumin conjugates.

To overcome these drawbacks PCT/US93/09766 contacts a chelating agent with poly(alkylene oxide) to form a metallizable polymer which, when associated with paramagnetic metal ions, provide polymeric chelates with improved utility as contrast agents for MR imaging. For example, such polymeric chelates contain relatively large amounts of metal, are potentially more stable in vivo, and are less immunoreactive than protein-chelate-metal complexes.

However, incorporation of the poly(alkylene oxide) moiety into the backbone of the polymer contributes to increased viscosity of the polymeric composition, thereby limiting formulation concentration and raising injection volume in order to maintain acceptable formulation viscosity.

Thus, it is readily apparent that it would be highly desirable to provide other polymeric MR contrast agents which also contain relatively large amounts of metal per molecule, i.e., are of high substitution ratios; are of a molecular weight enabling them to be circulated within the blood pool for extended periods of time; exhibit improved biodistribution for imaging blood vessels, body tumors and other tissues; yet yield low viscosity contrast compositions that maximize injectable concentration and minimize injectable volume.

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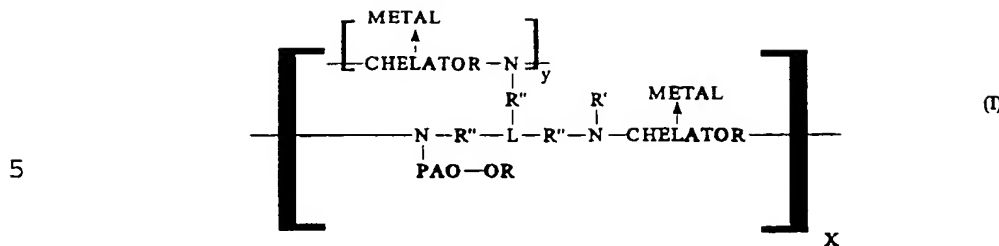
We have discovered that reactive α -(polyamino)poly-(alkylene oxides) can be contacted with chelating agents or precursors thereof containing reactive functionality to form metallizable graft co-polymers which, when
5 associated with paramagnetic metal ions, provide polymeric chelates of extraordinary utility as contrast agents for MR imaging. Such polymers have a more globular shape when compared to linear copolymers, resulting in decreased viscosity and increased
10 relaxivity.

We have also found that the use of polyamine linking groups with three or more amine groups introduces the potential for cross-linking and results in a polymer
15 with a more globular shape, thereby further decreasing viscosity and increasing relaxivity.

Thus viewed from one aspect the present invention provides a polymer for use as a contrast agent for
20 magnetic resonance imaging comprising a polymeric unit, said unit comprising the residue of a polyamine moiety linked to a chelating agent residue and to one or more pendant poly(alkylene oxides), preferably additionally to one or more pendant chelating agent residues via the
25 residue of a linking group.

More particularly the present invention provides a polymer for use as a contrast agent for MR imaging comprising a polymeric unit, wherein said unit comprises
30 a chelating agent residue linked to the residue of a polyamine moiety from which is subtended one or more pendant mono-functional polyalkylene oxides capped with H or alkoxy. The polymer, which may be linear or cross-linked, preferably comprises units having the structure
35 I:

- 6 -



wherein:

10 L and R'' = the residue of a linking group such as for example a polyamine

R = H or an alkyl group such as for example CH₃

R' = H, alkyl, aralkyl or -PAO-OR

PAO = a polyalkyleneoxide of MW 100-20,000

metal = any paramagnetic or radioactive metal species

15 chelator = a chelating agent residue preferably of DTPA, P4A, EDTA, etc.

y = 0-10

x = 2-1000

20 Viewed from a further aspect the present invention provides a pharmaceutical composition, preferably an MR imaging composition (hereinafter a "contrast agent"), comprising a polymer according to the invention together with one or more pharmaceutically acceptable carriers or
25 excipients.

Viewed from a yet further aspect the present invention provides a method of generating an enhanced MR image of the human or non-human animal body, said method
30 comprising administering to said body a contrast enhancing polymer according to the invention and generating an MR image of at least a part of said body into which said polymer distributes.

35 It is a particularly advantageous feature that the paramagnetic polymeric chelates of this invention provide effective MR contrast enhancement of the blood

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pool within the vascular system for remarkably long periods of time.

5 It is an advantageous feature of this invention that polymeric compounds are provided having a specificity toward accumulation in different tissues, for example, in tumors and the liver.

10 It is another advantageous feature of this invention that polymeric chelates suitable for MR imaging are provided containing relatively large amounts of metal that are potentially more stable in vivo and less immunoreactive than protein-chelate-metal complexes.

15 Yet another advantageous feature of this invention is that the molecular weight of the above-described polymers can be synthetically tailored to produce an agent of desired composition, molecular weight and size.

20 These agents also offer decreased viscosity (resulting from the substantially non-linear shape of the polymer) and increased relaxivity.

25 Still other advantageous features of this invention will become readily apparent upon reference to the following description of preferred embodiments. Reference is made to the accompanying drawings wherein:

30 Figure 1 is a plot of rabbit blood $1/T_1$ over time following intravenous administration of various compositions of this invention.

35 Figure 2 is a plot of proton relaxivity versus proton larmor frequency for various compositions of this invention and a comparative composition.

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Figures 3 and 4 show the results of an MR imaging experiment with one composition of this invention and two comparative agents.

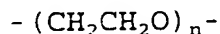
5 While the polymer of this invention is described herein primarily in connection with its preferred utilities, i.e., as a contrast agent for use in MR imaging, it also finds utility in other applications and fields. Thus
10 the polymers according to the invention have a variety of end uses e.g., as a therapeutic agent for example in radiotherapy and as an additive for paints, coatings and adhesives and as an antistatic agent for use in photographic and magnetic recording elements.

15 The polymer useful in the practice of the invention comprises units which comprise a chelating agent residue linked to the residue of a polyamine moiety in the backbone of the polymer chain with pendent chains of poly(alkylene oxide). The polymer preferably comprises
20 from 2 to 1000 or more, more preferably 3 to 1000, of the above described units. In especially preferred embodiments, the above-described units are recurring units.

25 In formula (I) above, PAO represents a linear or branched poly(alkylene oxide) moiety. Exemplary poly(alkylene oxide) moieties include poly(ethylene oxides), poly(propylene oxides) and poly(butylene oxides). Preferred poly(alkylene oxides) include poly-
30 (ethylene oxides) (PEO), poly(propylene oxides) (PPO) and random and block copolymers of PEO and PPO. PEO containing polymers are particularly preferred when it is desired for the final polymer to possess solubility in water. It is also contemplated that the poly(alkylene
35 oxide) moiety can comprise glycerol poly(alkylene oxide) triethers and linear and block copolymers of alkylene oxides with compatible comonomers such as poly-

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(ethyleneimine-co-ethylene oxide) and grafted block copolymers such as poly(methyl vinyl ether-co-ethylene oxide). For MR imaging applications, preferred poly(alkylene oxide) moieties have an average molecular weight in the range from about 100-20,000, more preferably 250-10,000 daltons. These moieties can be derived from poly(alkylene oxide) moieties which are commercially available in the corresponding diol form and/or can be prepared by techniques well known to those skilled in the art. A particularly preferred class of PEO moieties derived from PEGs can be represented by the structure:



wherein n is 2 to 5,000, preferably 2 to 2500, and more preferably 2 to 500.

The polymer of the invention can comprise the residue of one or more of a wide variety of chelating agents. As is well known, a chelating agent is a compound containing donor atoms that can combine by coordinate bonding with a metal atom to form a cyclic structure called a chelation complex or chelate. This class of compounds is described in the Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 5, 339-368.

The residues of suitable chelating agents can be selected from polyphosphates, such as sodium tripolyphosphate and hexametaphosphoric acid; aminocarboxylic acids, such as ethylenediaminetetraacetic acid, N-(2-hydroxyethyl) ethylenediaminetriacetic acid, nitrilotriacetic acid, N,N-di(2-hydroxyethyl)glycine, ethylenebis(hydroxyphenylglycine) and diethylenetriamine pentacetic acid; 1,3-diketones, such as acetylacetone, trifluoroacetylacetone, and thenoyltrifluoroacetone;

- 10 -

hydroxycarboxylic acids, such as tartaric acid, citric acid, gluconic acid, and 5-sulfosalicylic acid;
polyamines, such as ethylenediamine, diethylenetriamine, triethylenetetramine, and triaminotriethylamine;
5 aminoalcohols, such as triethanolamine and N-(2-hydroxyethyl)ethylenediamine;
aromatic heterocyclic bases, such as 2,2'-dipyridyl, 2,2'- diimidazole, dipicoline amine and 1,10-phenanthroline;
10 phenols, such as salicylaldehyde, disulfopyrocatechol, and chromotropic acid;
aminophenols, such as 8-hydroxyquinoline and oxinesulfonic acid;
oximes, such as dimethylglyoxime and salicylaldoxime;
15 peptides containing proximal chelating functionality such as polycysteine, polyhistidine, polyaspartic acid, polyglutamic acid, or combinations of such amino acids; Schiff bases, such as disalicylaldehyde 1,2-propylenediimine;
20 tetrapyrroles, such as tetraphenylporphin and phthalocyanine;
sulfur compounds, such as toluenedithiol, meso-2,3-dimercaptosuccinic acid, dimercaptopropanol, thioglycolic acid, potassium ethyl xanthate, sodium
25 diethyldithiocarbamate, dithizone, diethyl dithiophosphoric acid, and thiourea;
synthetic macrocyclic compounds, such as dibenzo(18)crown-6, $(CH_3)_6(14)4,11$ -diene N_4 , and (2.2.2-cryptate); and
30 phosphonic acids, such as nitrilotrimethylenephosphonic acid, ethylenediaminetetra(methylenephosphonic acid), and hydroxyethylidenediphosphonic acid,

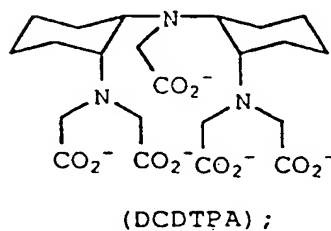
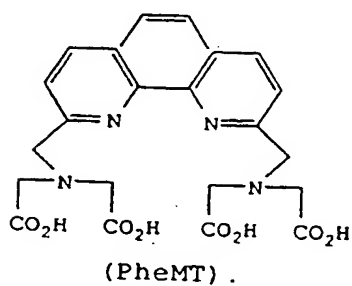
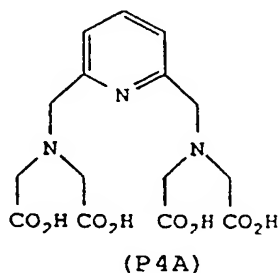
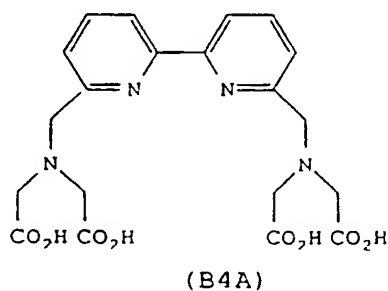
or combinations of two or more of the above agents.

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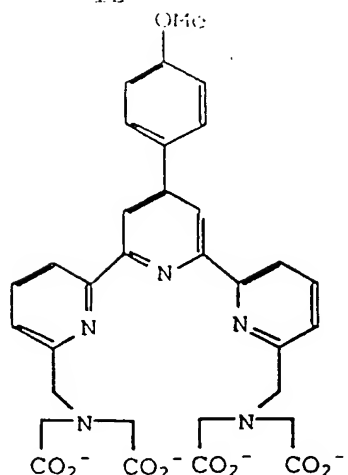
Preferred residues of chelating agents contain polycarboxylic acid groups and include: ethylenediamine-

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N, N, N', N'-tetraacetic acid (EDTA); N, N, N', N'', N'''-
 diethylenetriaminepentaacetic acid (DTPA); 1,4,7,10-
 tetraazacyclododecane-N, N', N'', N'''-tetraacetic acid
 (DOTA); 1,4,7,10-tetraazacyclododecane-N, N', N''-tri-
 5 acid (DO3A); 1-oxa-4,7,10-triazacyclododecane-N, N', N''-
 triacetic acid (OTTA); trans(1,2)-
 cyclohexanodiethylenetriamine pentaacetic acid (CDTPA)



-12-



(TMT) ;

- 5
- 10 Such chelating compounds, including their preparation and manipulation are well known in the art. Suitable chelating groups are described in PCT/US91/08253, the disclosure of which is hereby incorporated by reference. In formula I above, Z is the residue of one or more
- 15 chelating agents and the residue of the chelating agent is linked to the poly(amine) moiety through chemical bonds between the polyamine nitrogens and the chelator residue.
- 20 If the chelating residue is made of multiple chelating moieties or subunits, such subunits can be linked together by a linking group such as is described below. Thus, more than one chelating moiety can be used to make up the chelating residue. If more than one chelating
- 25 moiety is present in the chelating residue, these may be the same or different. Chelating moieties can be linked together using known chemistries. Thus the chelating residue can be one moiety or a "core" of chelating moieties. For example, a core of DTPA residues may be
- 30 prepared by reacting DTPA dianhydride with a diamine, such as ethylene diamine, to form a "core" of DTPA chelators. Other chelating residues, made up of multiple chelating moieties are well known in the art and are prepared by known chemistries as well.
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- For magnetic resonance imaging applications, the chelated metal ion preferably represents a paramagnetic

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metal ion such as an ion of metals of atomic number 21 to 29, 42, 44 and 57 to 71, especially 57 to 71. Ions of the following metals are preferred: Cr, V, Mn, Fe, Co, Ni, Cu, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm and Yb. Especially preferred are Cr^{3+} , Cr^{2+} , V^{2+} , Mn^{3+} , Mn^{2+} , Fe^{3+} , Fe^{2+} , Co^{2+} , Gd^{3+} and Dy^{3+} particularly especially preferably Gd^{3+} , Fe^{3+} , Mn^{2+} , Mn^{3+} , Dy^{3+} and Cr^{3+} . It is a particularly advantageous feature that polymers can be provided exhibiting a high substitution ratio, i.e., containing relatively large numbers of paramagnetic metal ions per molecule.

For radiotherapy, the therapeutic agent can be a radioactive isotope, preferably a radioactive metal ion isotope. This radioactive metal isotope can be an ion of an isotope of a metal selected, for example, from Sc, Fe, Pb, Ga, Y, Bi, Mn, Cu, Cr, Zn, Ge, Mo, Tc, Ru, In, Sn, Re, Sr, Sm, Lu, Du, Sb, W, Re, Po, Ta and Tl ions. In a preferred embodiment, radioisotopes which are also useful in diagnostic imaging applications are specifically contemplated. Thus this embodiment finds utility in imaging and therapy where either procedure can be performed in conjunction with or ancillary to the other. Preferred isotopes of radioactive metal ions for this embodiment include ^{44}Sc , ^{64}Cu , ^{67}Cu , ^{111}In , ^{212}Pb , ^{68}Ga , ^{90}Y , ^{153}Sm , ^{212}Bi , $^{99\text{m}}\text{Tc}$ and ^{188}Re for therapeutic and diagnostic imaging applications.

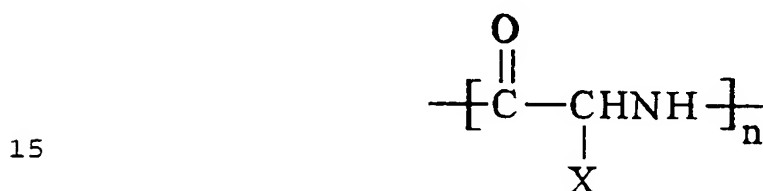
The group R" denotes the residue of a linking group such as a polyamine and may include:

hydrogen, alkylene, preferably C_{1-18} -alkylene such as methylene, ethylene, propylene, butylene and hexylene, such alkylene optionally being interrupted by 1 or more heteroatoms such as oxygen, nitrogen and sulfur or heteroatom-containing groups.

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The linking group L may include:

carbon; nitrogen; carbonyl; sulfonyl; sulfinyl; ether;
thioether; ester, i.e., carbonyloxy and oxycarbonyl;
thioester, i.e., carbonylthio and thiocarbonyl; amide,
5 i.e., iminocarbonyl and carbonylimino; thioamide, i.e.,
iminothiocarbonyl and thiocarbonylimino; thio; dithio;
phosphate; phosphonate; urelene; thiourelene; urethane,
i.e., iminocarbonyloxy; thiourethane, i.e.,
iminothiocarbonylthio; an amino acid linkage, i.e., a
10 group



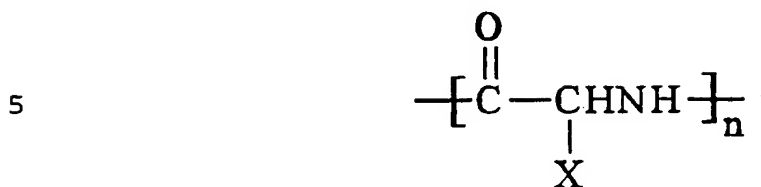
or



wherein $n=1$ and X is H, alkyl, containing from 1 to 18,
25 preferably 1 to 6 carbon atoms, such as methyl, ethyl
and propyl, such alkyl optionally being interrupted by 1
or more heteroatoms such as oxygen, nitrogen and sulfur,
substituted or unsubstituted aryl, containing from 6 to
18, preferably 6 to 10 carbon atoms such as phenyl,
30 hydroxyiodophenyl, hydroxyphenyl, fluorophenyl and
naphthyl, aralkyl, preferably containing from 7 to 12
carbon atoms, such as benzyl, heterocyclyl, preferably
containing from 5 to 7 nuclear carbon and one or more
heteroatoms such as S, N, P or O, examples of preferred
35 heterocyclyl groups being pyridyl, quinolyl, imidazolyl
and thienyl; heterocyclylalkyl, the heterocyclyl and
alkyl portions of which preferably are described above;

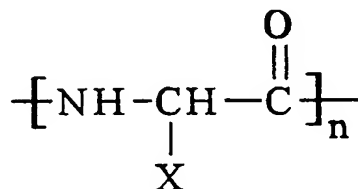
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or a peptide linkage, i.e., a group



or

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wherein $n > 1$ and each X independently is represented by a group as described for X above. Two or more linking groups can be used, such as, for example, alkyleneimino and iminoalkylene. It is contemplated that other linking groups may be suitable for use herein, such as linking groups commonly used in protein heterobifunctional and homobifunctional conjugation and crosslinking chemistry. Especially preferred linking groups are unsubstituted or substituted imino groups which when linked to the carbonyl in the residue of a chelating agent form an amide.

20

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The linking groups can contain various substituents which do not interfere with the polymerization reaction. The linking groups can also contain substituents which can interfere with the polymerization reaction, but which during the polymerization reaction, are prevented from so doing with suitable protecting groups commonly known in the art and which substituents are regenerated after the polymerization by suitable deprotection. The linking groups can also contain substituents that are

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introduced after the polymerization. For example, the linking group can be substituted with substituents such as halogen, such as F, Cl, Br or I; an ester group; an amide group; alkyl, preferably containing from 1 to about 18, more preferably 1 to 4 carbon atoms such as methyl, ethyl, propyl, i-propyl, butyl, and the like; substituted or unsubstituted aryl, preferably containing from 6 to about 20, more preferably 6 to 10 carbon atoms such as phenyl, naphthyl, hydroxyphenyl, iodophenyl, hydroxyiodophenyl, fluorophenyl and methoxyphenyl; substituted or unsubstituted aralkyl, preferably containing from 7 to about 12 carbon atoms, such as benzyl and phenylethyl; alkoxy, the alkyl portion of which preferably contains from 1 to 18 carbon atoms as described for alkyl above; alkoxyaralkyl, such as ethoxybenzyl; substituted or unsubstituted heterocyclyl, preferably containing from 5 to 7 nuclear carbon and heteroatoms such as S, N, P or O, examples of preferred heterocyclyl groups being pyridyl, quinolyl, imidazolyl and thienyl; a carboxyl group; a carboxyalkyl group, the alkyl portion of which preferably contains from 1 to 8 carbon atoms; the residue of a chelating group, preferably such as described for Z above; or a poly(alkylene oxide) moiety, preferably such as described for Q above.

The metal content in the metallised polymer of the invention can vary from about 0.1 up to about 30% based on the total weight of the polymer. For MR imaging, the polymer preferably contains the paramagnetic metal in an amount of from 1 to 25%, more preferably 2-20% by weight. In a therapeutic embodiment the radionuclide metal ion is present in roughly the same amounts as for imaging.

35

For MR imaging, the polymer preferably comprises from 2 to about 500, more preferably 5 to 100 recurring units.

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If the polymer contains a peptide that can be hydrolyzed, then the polymer can contain from 1 to several hundred paramagnetic metal ions per molecule.

5 The polymer in structure (I) can be capped at the termini with groups independently selected from Z or hydrogen. In preferred embodiments, wherein the polymer is a polyamide, the polymer can be capped with groups such as hydrogen or hydroxyl groups or with groups
10 derived from polyamide chain terminating agents such as monoamines and monoacyl derivatives such as monoanhydrides, e.g., acetic anhydride, or with groups derived from the residue of a chelating group as defined above. It is further contemplated that cyclic polymers,
15 i.e., non-capped polymers can be prepared.

The polymer of this invention can be prepared in water-soluble, water-dispersible or water-insoluble forms depending upon the intended application. The polymer can
20 be crosslinked or non-crosslinked. The molecular weight of the polymer can vary widely, i.e., from about 1,000 to 10^8 or greater, as measured by gel permeation chromatography (GPC). The water-soluble polymer preferably is of molecular weight from 1,000 to about
25 250,000. For MR imaging; the polymer preferably is of molecular weight 5,000- 10^6 , more preferably 10,000-100,000.

The polymer of this invention can be prepared by
30 contacting a reactive poly(alkylene oxide) species with a chelating agent or precursor thereof containing reactive functionality in a non-reactive solvent to form the polymer. The poly(alkylene oxide) can be substituted or unsubstituted.

35 The preferred reaction conditions, e.g., temperature, pressure, solvent, etc., depend primarily on the

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particular reactants selected and can be readily determined by one skilled in the art.

Thus viewed from a yet still further aspect the present invention provides a process for the preparation of a polymer according to the invention, said process comprising one or more of the following steps:

- (a) reacting a poly(alkylene oxide) or a derivative thereof with a chelating agent or precursor therefor containing reactive functionality;
- (b) a condensation polymerisation reaction between a polyamine and a diacid containing the metallised chelating group or an activated derivative thereof;
- (c) protecting the reagents of either of steps (a) or (b) with suitable protecting groups and subsequently removing said protecting groups.

Suitable reactive poly(alkylene oxide) species include α -(polyamino)-poly(alkylene oxides), α -(polyhydrazino)poly(alkylene oxides), α -(polyisocyanato)-poly(alkylene oxides), α -(polyhydroxy)-poly(alkylene oxides), α -poly(aldehydic)-poly(alkylene oxides), α -(polycarboxy)-poly(alkylene oxides), α -(poly[vinyl sulphonyl])-poly(alkylene oxides), α -(polyphosphato)-poly(alkylene oxides), α -(poly-[N, N-dialkylaminophosphoramidato])-poly(alkylene oxides), α -(polyoxirano)-poly(alkylene oxides), α -(polyalkoxy)-poly(alkylene oxides), α -(polysulphonato)-poly(alkylene oxides), and the like.

The above-described poly(alkylene oxide) species are linear polymers containing multi-functionality at one end of the polymer and no reactive functionality at the opposite end; branched poly(alkylene oxide) species relating to the above containing multi-functionality at one end of the polymer only are also useful.

Suitable chelating agents and precursors thereof

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containing reactive functionality include polycarboxylic acids in dianhydride form, di(sulfonyl chlorides), di(alkyl sulfates), di(vinyl sulfones), and the like. As will be recognized by one skilled in the art, a suitably blocked pregenitor to the chelating agent or precursor thereof containing reactive functionality can be contacted with the reactive poly(alkylene oxide) moiety to form the polymer, and then the blocking group can be subsequently removed by techniques known in the art. It is contemplated that additional chelating functional groups can be introduced by suitable chemical modification at the unblocked sites. If hydroxy substituents are to be selectively present in the final polymer, they must be temporarily blocked during polymerization, e.g., by conventional blocking techniques to minimize formation of undesirable by-products, e. g., polyesteramide derived therefrom. However, for some purposes, polyesterpolyamides which contain one or more ester linking groups in the backbone of the polymer are contemplated to be useful.

In a preferred embodiment, the polymer of this invention can be prepared by reacting a linear α -(polyamino)-poly(alkylene oxide) with a precursor of a chelating agent in an internal dianhydride form.

The α -(polyamino)-poly(alkylene oxide) can be prepared by reacting an activated form of the poly(alkylene oxide) with a polyamine. The polyamino group can be introduced by other methods known in the art. Suitable illustrative polyamines include diaminohexane, tris(aminoethyl)amine, and diethylenetriamine.

The linear poly(alkylene oxide) in its α -hydroxy- ω -methoxy form is widely available commercially or can be prepared by techniques well known to those skilled in the art. The poly(alkylene oxide) is activated for

- 20 -

nucleophilic displacement by reacting it with an activator such as p-toluenesulfonyl chloride, thionyl chloride, thionyl bromide, an alkylsulfonyl chloride, e.g., $\text{CH}_3\text{SO}_2\text{Cl}$, a sulfonic acid anhydride, or any other
5 suitable activator known in the art. The activated form of the poly(alkylene oxide) thus can be a tosylate, a chloride, a bromide, etc.

The activated form of the poly(alkylene oxide) is
10 reacted preferably with a stoichiometric excess of the polyamine, in an inert solvent preferably at a temperature, e.g., 100-160°C, and pressure, e.g., 1 to 10 atmospheres, sufficient to drive the reaction to completion. Suitable solvents include dioxane, ethanol,
15 and other alcohols. Thereafter, the α -(polyamino)poly(alkylene oxide) preferably is isolated, e.g., by evaporation or precipitation, and purified, e.g., by dissolving in a suitable solvent such as methylene chloride, chloroform or trichloroethane, and then
20 washing the solution with an excess of aqueous NaOH, or by any other suitable isolation and purification techniques.

The internal anhydride forms of the chelating agents
25 described above are commercially available and/or can be prepared by techniques known in the art. For example, the internal anhydride forms of EDTA and DTPA are commercially available. The internal anhydride forms of B4A, P4A and TMT can be prepared by techniques known in
30 the art. For example, the anhydrides can be prepared by heating the corresponding acids in acetic anhydride in the presence of pyridine as catalyst. Methods for the preparation of B4A, P4A and TMT are described in U.S. Patent 4,859,777. Mixed anhydrides are also suitable.

35

The reactive α -(polyamino)-poly(alkylene oxide) can be reacted with the internal dianhydride in a non-reactive

- 21 -

solvent to form the unmetallized polymer. The reaction conveniently can take place at approximately room temperature and atmospheric pressure. However, higher and lower temperatures and pressures are contemplated.

5 Suitable solvents include dimethylsulfoxide, dimethylformamide, acetonitrile, chloroform, dichloromethane and 1,2-dichloroethane. The non-metallized polymer preferably is isolated and then purified, e.g., by diafiltration.

10

The metallized polymer can be formed by contacting the unmetallized polymer with a source of metal ions. This can be conveniently accomplished by adding a solution of or a solid salt or oxide of the metal to a solution, preferably an aqueous solution, of the polymer.

15

Thereafter, the chelated polymer preferably is diafiltered in water to remove excess unchelated metal.

20

A general reaction scheme for this method of preparing the polymers of this invention and illustrative examples are set forth below.

25

Alternatively, the polymer can be prepared in a condensation polymerization reaction between a suitable polyamine and a diacid containing the metallized chelating group, in a suitably activated form, e.g., in the form of an activated diester.

30

The molecular weight of the polymer product depends upon many factors including, for example, the molecular weight of the starting poly(alkylene oxide) moiety, the presence or absence of reactive polymerization chain terminating agents such as monoanhydrides or monoamines in the case of polyamides which reduce molecular weight by end-capping the polymer during the polymerization process, the presence or absence of reactive crosslinkers which increase the molecular weight of the

35

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polymer during polymerization, and the relative concentrations of the poly(alkylene oxide) and chelator present during the polymerization reaction which in turn affects the number of recurring units in the polymer product. The preparation of insoluble and water-soluble polymers of molecular weight 1,000 to 10^8 can be accomplished by routine experimentation by one skilled in the art of polymer synthesis techniques.

The polymer preferably is prepared in a water soluble, i.e., injectable form when used as an MR contrast agent for blood pool imaging or as a composition intended to be administered intravenously. On the other hand, the polymer can be prepared preferably as a water-insoluble polymer when intended to be administered orally as an MR contrast agent for gastro-intestinal imaging.

Where the copolymer comprises a chelated toxic metal species, eg. a heavy metal ion, it may be desirable to include within the formulation a slight excess of a chelating agent, eg. as discussed by Schering in DE-A-3640708, or more preferably a slight excess of the calcium salt of a chelating agent.

Actual levels of active ingredient in administered compositions of the present invention may be varied so as to obtain an amount of active ingredient that is effective to obtain the desired effect for a particular composition and method of administration. The selected dosage level therefore depends upon the desired effect, on the route of administration, on the desired duration of treatment and other commonly considered factors.

The dosages of the contrast agent used according to the present invention will vary according to the precise nature of the contrast agent used. Preferably however, the dosage should be kept as low as is consistent with

- 23 -

achieving contrast enhanced imaging and volumes minimized for IV drip or bolus injection. In this way, the toxicity potential is minimized. For most MR contrast agents the appropriate dosage will generally
5 range from 0.02 to 3 mmol paramagnetic metal/kg body weight, especially 0.05 to 1.5 mmol/kg, particularly 0.08 to 0.5, more especially 0.1 to 0.4 mmol/kg. It is well within the skill of the average practitioner in this field to determine the optimum dosage for any
10 particular MR contrast agent by relatively routine experimentation, for both in vivo or in vitro applications.

Contrast agents may be formulated with conventional
15 pharmaceutical or veterinary aids, for example stabilizers, antioxidants, osmolality adjusting agents, buffers, pH adjusting agents, etc., and may be in a form suitable for injection or infusion directly or after dispersion in or dilution with a physiologically
20 acceptable carrier medium, e.g., water for injection. Thus the contrast agents may be formulated in conventional administration forms such as powders, solutions, suspensions, dispersions, etc., however
25 solutions, suspensions and dispersions in physiologically acceptable carrier media will generally be preferred.

The contrast agents may be formulated for administration using physiologically acceptable carriers or excipients,
30 for parenteral injection, for oral administration in solid or liquid form, for rectal or topical administration or the like in a manner fully within the skill of the art. For example, the compounds, optionally with the addition of pharmaceutically acceptable
35 excipients, may be suspended or dissolved in an aqueous medium, with the resulting solution or suspension then being sterilized.

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Parenterally administrable forms, e.g., intravenous solutions, should of course be sterile and free from physiologically unacceptable agents, and should have low osmolality to minimize irritation or other adverse effects upon administration and thus the contrast medium should preferably be isotonic or slightly hypertonic. Suitable vehicles include aqueous vehicles customarily used for administering parenteral solutions such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection and other solutions such as are described in Remington's Pharmaceutical Sciences, 15th ed., Easton: Mack Publishing Co., pp. 1405-1412 and 1461-1487 (1975) and The National Formulary XIV, 14th ed. Washington: American Pharmaceutical Association (1975). The solutions can contain preservatives, antimicrobial agents, buffers and antioxidants conventionally used for parenteral solutions, excipients and other additives which are compatible with the contrast agents and which will not interfere with the manufacture, storage or use of products.

Thus viewed from a yet still further aspect the present invention provides a method of therapy practised on the human or non-human animal body, which method comprises administering to said body a therapeutically effective polymer according to the invention, for example a therapeutically effective chelated metal.

Viewed from an even further aspect, the present invention also provides the use of the polymers according to the invention for the manufacture of diagnostic or therapeutic agents for use in methods of image generation or therapy practised on the human or non-human animal body.

- 25 -

Viewed from a still further aspect, the present invention provides a process for the preparation of a chelated metal bearing polymer, said process comprising metallating a chelating moiety containing polymer according to the invention, eg. by admixing the polymer in a solvent together with an at least sparingly soluble compound of the metal, for example a chloride, oxide, acetate or carbonate.

The following Examples are intended to further illustrate the invention in a non-limiting manner.

Examples 1-4 describe the preparation of a cross-linked polymer (Ia) prepared from methoxypolyethylene glycol of average MW 2000 in which:

L and R" = N(CH₂CH₂NH₂)₃

R = CH₃

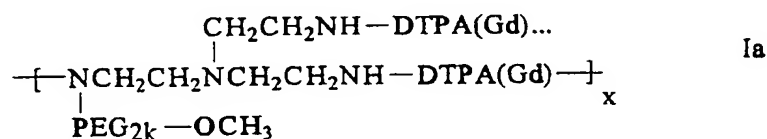
PAO = Polyethylene glycol

metal = Gd(III)

chelator = DTPA

y = 1

x = 4.2 (average)



Examples 5-8 and 9-12 describe analogous cross-linked polymers (Ib and Ic respectively) prepared from methoxypolyethylene glycols of average MW 750 and 550, respectively, wherein:

L and R" = N(CH₂CH₂NH₂)₃

R = CH₃

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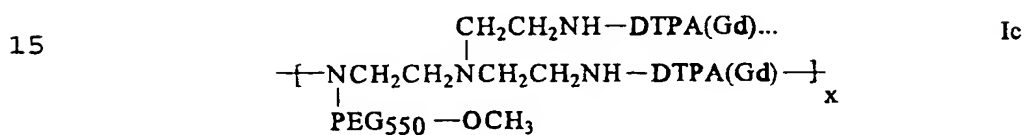
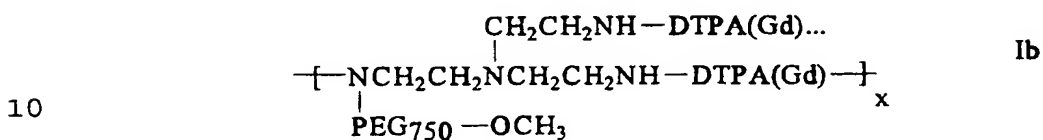
PAO = Polyethylene glycol

metal = Gd(III)

chelator = DTPA

y = 1

5 x = 11.7 (average) and 9.3 (average), respectively



20 Examples 13-15 describe a linear polymer (Id) in which:

L and R" = H₂NCH₂CH₂(OCH₂CH₂)₂NH₂R = CH₃

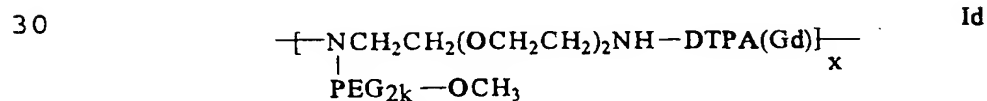
PAO = Polyethylene glycol

metal = Gd(III)

25 chelator = DTPA

y = 0

x = 3.3 (average)

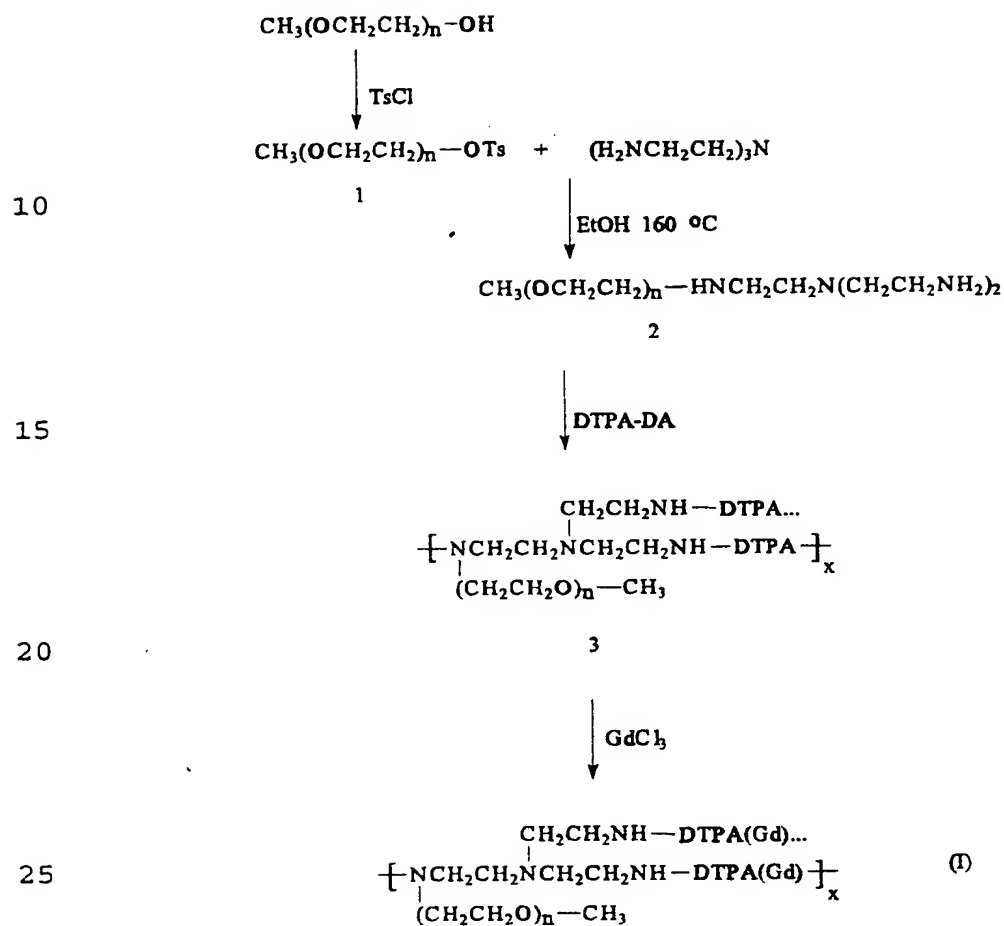


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Polymers Ia, Ib and Ic were prepared as illustrated in scheme 1:

SCHEME 1

5

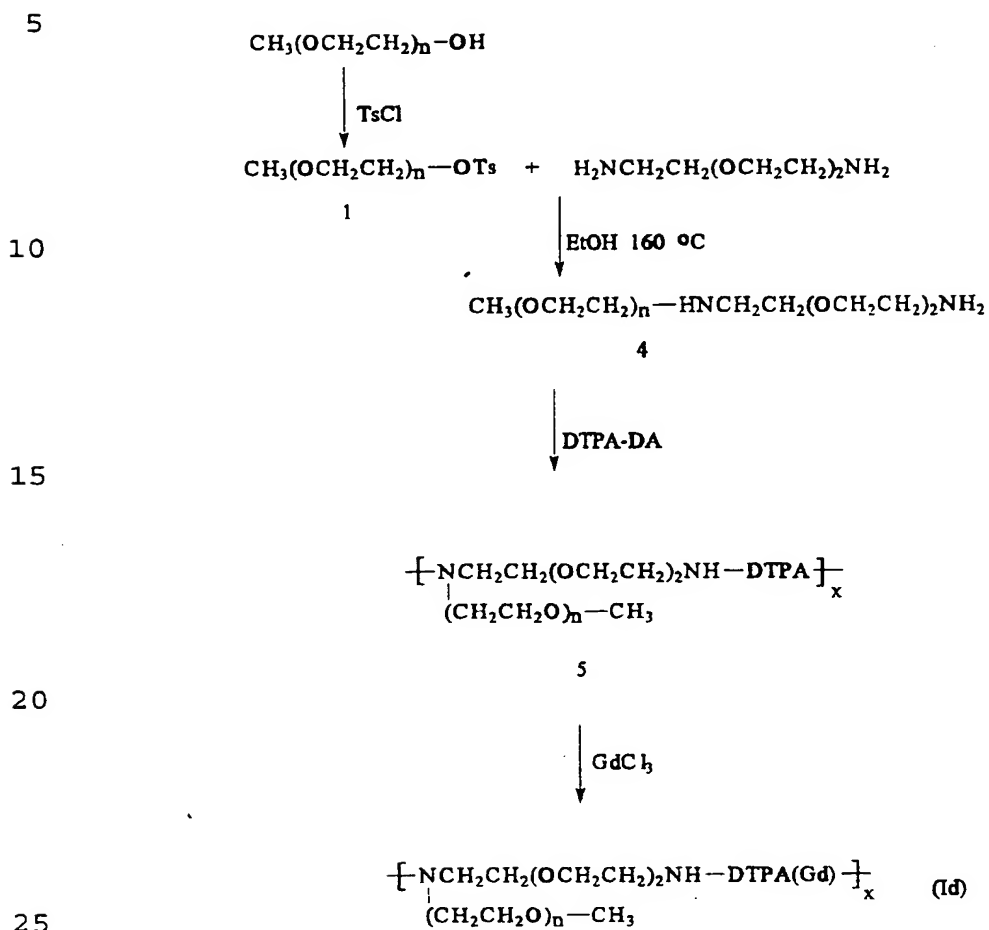


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30      n = 1 to 5000
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Polymer Id was prepared as illustrated in scheme 2:

SCHEME 2



n = 1 to 5000

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Example 1

A solution of methoxy-PEG of average MW 2000 (44.20 g, 22.1 mmol; Union Carbide) in 663 ml of toluene was
5 refluxed with azeotropic removal of water for several hours. The cooled toluene solution was treated with triethylamine (7.39 ml, 53.0 mmol), 4-dimethylaminopyridine (0.270 g, 2.21 mmol) and tosyl chloride (9.27 g, 48.6 mmol) and heated in an oil bath
10 at 60°C for 48 hours. An additional 3.70 ml of triethylamine, 0.135 g of dimethylaminopyridine and 4.64 g of tosyl chloride was added and heating continued at 60°C for 144 hours. An additional 3.70 ml of
15 triethylamine, 0.135 g of dimethylaminopyridine and 4.64 g of tosyl chloride was added and heating continued at 60°C for another 144 hours. The reaction mixture was then cooled and filtered. The filtrate was extracted three times with water. The combined aqueous extracts were washed three times with ether, then extracted three
20 times with chloroform. The chloroform extracts were dried over anhydrous MgSO_4 and concentrated to 40.65 g (85%) of product 1a.

Example 2

25 A solution of 24.87 g (11.55 mmol) of 1a in 250 mls of absolute EtOH was treated with 17.3 ml (115 mmol) of tris(2-aminoethyl)amine. The reaction mixture was heated in a stainless steel bomb at 160°C for 16 hours. The
30 solvent was removed by evaporation and the residue dissolved in 500 ml of water and made basic with 23 ml of 1N NaOH. The basic solution was washed twice with ether, then extracted with chloroform. The chloroform extracts were dried over anhydrous MgSO_4 ; solvent
35 evaporation followed by heating at 90°C under vacuum (1 mm) to remove residual tris(2-aminoethyl)amine yielded 23.94 g (97%) of 2a.

- 30 -

Example 3

A solution of 3.99 g (1.88 mmol) of 2a in 40 mls of acetonitrile was treated with triethylamine (0.784 ml, 5.62 mmol) and diethylenetriaminepentaacetic acid dianhydride (1.005 g, 2.81 mmol). After 3.25 hours at room temperature acetic anhydride 0.18 ml (1.9 mmol) was added and stirring continued for an additional 30 min., then 160 ml of water was added.

10

Example 4

The solution of crude polymer 3a from Example 3 was treated with gadolinium(III) chloride hexahydrate (1.15 g, 3.09 mmol) then diafiltered against water in a diafiltration cell equipped with a 10,000 MW cut-off membrane. The pH of the solution was adjusted to 7 with NaOH then the solution was filtered through a 0.2 mm nylon filter. Lyophilization yielded 2.81 g of product (Ia) of average molecular weight 12,100 daltons as determined by SEC-HPSC using PEG molecular weight standards; 7.60% gadolinium by weight.

15
20

Intravenous administration of 100, 300 and 1000 mmol Gd/Kg of a 100 mM Gd solution of Ia in isotonic saline to mice resulted in no deaths and no abnormalities upon necropsy after 7 days.

25

Example 5

30

A solution of methoxy-PEG of average MW 750 (100.0 g, 0.1333 mol; Sigma Chemical Co.) in 1500 ml of toluene was refluxed with azeotropic removal of water for several hours. The cooled toluene solution was treated with triethylamine (61.3 ml, 0.440 mol), 4-dimethylaminopyridine (1.62 g, 0.0133 mol) and tosyl chloride (76.26 g, 0.400 mol) and heated in an oil bath

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at 60°C for 48 hours. The cooled reaction mixture was work up as described in Example 1 to yield 100.4 g (83%) of product 1b.

5 Example 6

Product 1b from Example 5 was reacted with tris(2-aminoethyl)amine as described in Example 2 to give a 97% yield of 2b.

10

Example 7

A solution of 5.39 g (6.14 mmol) of 2b in 54 mls of acetonitrile was treated with triethylamine (2.57 ml, 18.4 mmol) and diethylenetriaminepentaacetic acid dianhydride (3.29 g, 9.20 mmol). After 1.0 hour at room temperature 216 mls of water was added and the solution stirred for 30 min.

15

20 Example 8

The solution of crude polymer 3b from Example 7 was treated with gadolinium(III) chloride hexahydrate (3.76 g, 10.1 mmol) then diafiltered against water in a diafiltration cell equipped with a 10,000 MW cut-off membrane. The pH of the solution was adjusted to 7 with NaOH then the solution was filtered through a 0.2 mm nylon filter. Lyophilization yielded 6.05 g of product (1b) of average molecular weight 19,100 daltons as determined by SEC-HPSC using PEG molecular weight standards; 13.1% gadolinium by weight.

25

30

Intravenous administration of 100, 300 and 1000 mmol Gd/Kg of a 100 mM Gd solution of 1b in isotonic saline to mice resulted in no deaths, no clinical signs and no abnormalities upon necropsy after 7 days.

35

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Example 9

A solution of methoxy-PEG of average MW 550 (66.67 g, 0.1212 mol; Sigma Chemical Co.) in 1000 ml of toluene
5 was refluxed with azeotropic removal of water for several hours. The cooled toluene solution was treated with triethylamine (55.75 ml, 0.4000 mol), 4-dimethylaminopyridine (2.96 g, 0.0242 mol) and tosyl chloride (69.33 g, 0.3636 mol) and heated in an oil bath
10 at 60°C for 48 hours. The cooled reaction mixture was work up as described in Example 1 to yield 47.58 g (56%) of product 1c.

Example 10

15 Product 1c from Example 9 was reacted with tris(2-aminoethyl)amine as described in Example 2 to give a 84% yield of 2c.

20 Example 11

A solution of 4.23 g (6.24 mmol) of 2c in 42 mls of acetonitrile was treated with triethylamine (2.61 ml, 18.7 mmol) and diethylenetriaminepentaacetic acid
25 dianhydride (3.34 g, 9.36 mmol). After 1.0 hour at room temperature 168 mls of water was added and the solution stirred for 30 min.

Example 12

30 The solution of crude polymer 3c from Example 11 was treated with gadolinium(III) chloride hexahydrate (3.65 g, 9.83 mmol) then diafiltered against water in a diafiltration cell equipped with a 10,000 MW cut-off
35 membrane. The pH of the solution was adjusted to 7 with NaOH then the solution was filtered through a 0.2 mm nylon filter. Lyophilization yielded 4.15 g of product

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(Ic) of average molecular weight 13,600 daltons as determined by SEC-HPLC using PEG molecular weight standards; 15.6% gadolinium by weight.

- 5 Intravenous administration of 100, 300 and 1000 mmol Gd/Kg of a 100 mM Gd solution of Ic in isotonic saline to mice resulted in no deaths, no clinical signs and no abnormalities upon necropsy after 7 days.

10 Example 13

- Product 1a from Example 1 was reacted with "ED-148" as described in Example 2 to give 4 in 75% yield after precipitation of a methylene chloride solution with
15 ether.

Example 14

- A solution of 1.45 g (0.680 mmol) of 4 in 14.5 mls of
20 acetonitrile was treated with triethylamine (0.190 ml, 1.36 mmol) and diethylenetriaminepentaacetic acid dianhydride (0.267 g, 0.748 mmol). After 4 hours at room temperature 58 mls of water was added.

25 Example 15

- The solution of crude polymer 5 from Example 14 was treated with gadolinium(III) chloride hexahydrate (0.215 g, 0.578 mmol) then diafiltered against water in a
30 diafiltration cell equipped with a 5,000 MW cut-off membrane. The solution was filtered through a 0.45 mm nylon filter and lyophilised to yield 1.06 g of product (Id) of average molecular weight 8,700 daltons as determined by SEC-HPLC using PEG molecular weight
35 standards.

Viscosity Measurements. Viscosities of aqueous solutions

- 34 -

of Ia (Example 4), Ib (Example 8), Ic (Example 12) and a linear copolymer of similar molecular weight prepared from polyethylene glycol(1450)-diamine and DTPA [PEG(1450)-DTPA(Gd)] are shown in Table 1. The compound
 5 is disclosed in PCT/US93/09766. The viscosities were measured with a Brookfield viscometer (Model LVCP DVII-plus) equipped with a cone and plate spindle and a jacketed sample cell for temperature control. The
 10 temperature was controlled with a LAUDA RM6 circulating water bath. The viscometer was calibrated using Brookfield viscosity standards that ranged from 5-100 cP

Table 1. Polymeric Gd-Chelate Viscosities

Polymer	Concentration		Viscosity
	mg Polymer/ml	mM Gd	cP @ (°C)
Ia(Example 4)	210.	100.	13.5 (20°C)
Ib(Example 8)	120.	100.	5.3 (20°C)
Ic(Example 12)	100.	100.	2.2 (25°C)
	149.	147.	3.3 (25°C)
	199.	196.	5.1 (25°C)
PEG(1450)-DTPA(Gd)	104.	46.0	9.1 (20°C)
	120.	53.1	11.6 (20°C)
	210.	92.9	45.3 (20°C)
	226.	100.0	56.1 (20°C)

30

The data shows that the compositions of this invention produce solutions of very low viscosity. For example, the viscosities of 100 mM Gd solutions of Ia (13.5 cP), Ib (5.3 cP) and Ic (2.2 cP) are much lower than a 100 mM
 35 solution of polymeric PEG(1450)-DTPA(Gd) (56.1 cP). The compositions of this invention are also significantly less viscous than polymeric PEG(1450)-DTPA(Gd) when

- 35 -

compared at equal mg polymer/ml concentrations: 13.5 cP for Ia vs. 45.3 cP for polymeric PEG(1450)-DTPA(Gd) at 210 mg polymer/ml and 5.3 cP for Ib vs. 11.6 cP for polymeric PEG(1450)-DTPA(Gd) at 120 mg polymer/ml.

5

Determination of Blood Pool Retention in Rabbits

Rabbits were prepared with surgically implanted percutaneous catheters in the lateral ear vein.

10 Formulations of polymers Ia (Example 4), Ib (Example 8) and Ic (Example 12) containing 100 mM Gd in isotonic saline were injected into the opposite ear of the rabbit at a dose of 0.06 mmol Gd/Kg. Blood samples were withdrawn through the catheter and collected in heparin

15 tubes at 0, 5, 15, 30, 60 minutes, 2 hours and 24 hours following the injection. T_1 measurements were made on the blood samples using a Bruker MiniSpec operating at 20 MHz and 40°C. The data is presented graphically in figure 1.

20

The data shows that administering the compositions of this invention to rabbits results in significant increases in blood $1/T_1$ for at least 120 minutes. Prolonged blood $1/T_1$ enhancement makes these agents

25 useful for vascular imaging as exemplified in Figures 3 and 4.

Nuclear Magnetic Resonance Dispersion Curves

30 NMRD curves were obtained for polymers Ia (Example 4), Ib (Example 8) and Ic (Example 12) at 35°C. The data is presented graphically in figure 2 along with comparative data for polymeric PEG(1450)-DTPA(Gd), a compound disclosed in PCT/US93/09766. The results demonstrate the

35 improved relaxivities of the compositions of this invention in comparison with the linear polymer PEG(1450)-DTPA(Gd). The improvement in relaxivity is

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particularly noteworthy at proton Larmor frequencies in the 20 to 60 MHz range; corresponding to the commonly employed clinical magnet field strengths of 0.5-1.5 Tesla.

5

MR IMAGING STUDIES

The composition of Example 12, polymeric PEG(1450)-DTPA(Gd) (a comparative compound of similar molecular weight disclosed in PCT/US93/09766) and Magnevist® (a commercial non-polymeric comparison) were imaged in normal male New Zealand White Rabbits (3 rabbits/dose) employing 3D-TOF MR angiography of the abdominal vasculature at 1.5T (GE Signa, Milwaukee, WI) pre and post-contrast administration. Imaging parameters were: Field of view (FOV) = 24 cm, axial acquisition, Repetition time (TR) = 33, 3 mm slice thickness, 60 partitions, 256x256 matrix, and 1 excitation (1 NEX). At 5 minutes post injection, MRA was performed with the above parameters and a 30° flip angle; immediately following this sequence (15 minutes post injection), MRA was performed with the same parameters and a 90° flip angle. Region-of-interest (ROI) measurements were performed of the high (intrahepatic) and mid inferior vena cava (IVC) and of paraspinal musculature on both pre- and post-contrast sequences. Three ROI measurements were performed at both IVC levels and averaged to yield a single value. Percent contrast with background was computed as $100 (SI_{IVC} - SI_{MUSCLE}) / SI_{MUSCLE}$ (SI = signal intensity). The results are shown graphically in Figures 3 and 4.

As indicated by the graphs in Figures 3 and 4, the representative composition of this invention exhibits outstanding enhancement of the vasculature particularly in comparison with the low molecular weight agent Magnevist®. In addition, %Contrast (high (intrahepatic)

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and mid inferior vena cava (IVC) versus paraspinal musculature) is comparable to the linear polymer PEG(1450)-DTPA(Gd) at lower dose (0.056 mmol Gd/Kg vs. 0.08 mmol Gd/Kg).

5

The invention has been described in detail with particular reference to certain preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and

10

scope of the invention.

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Claims:

1. A polymer for use as a contrast agent for magnetic resonance imaging comprising a polymeric unit, said unit comprising the residue of a polyamine moiety linked to a chelating agent residue and to one or more pendant poly(alkylene oxides).

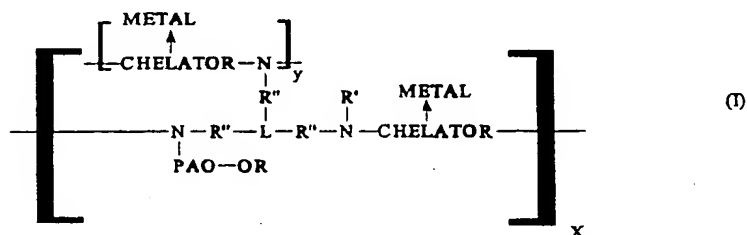
2. A polymer as claimed in claim 1 wherein said unit additionally comprises one or more pendent chelating agent residues linked to the polymer backbone via the residue of a linking group.

3. A polymer as claimed in either of claims 1 or 2 wherein said chelating agent residue has a paramagnetic or radioactive metal species associated therewith.

4. A polymer as claimed in any of the preceding claims comprising polymeric units of formula (I):

20

25



wherein L and R'' = the residue of a linking group;
 30 R = H or an alkyl;
 R' = H, alkyl, aralkyl or -PAO-OR;
 PAO = a polyalkyleneoxide of MW 200-20,000;
 metal = a paramagnetic or radioactive metal species;
 chelator = a chelating agent residue;
 35 y = 0-10; and
 x = 2-1000.

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5. A polymer as claimed in claim 4 wherein said groups L and R" are residues of a polyamine.

6. A polymer as claimed in any of claims 3 to 5
5 wherein said metal species is selected from the group consisting of Gd^{3+} , Fe^{3+} , Mn^{2+} , Mn^{3+} , Dy^{3+} and Cr^{3+} .

7. A polymer as claimed in any preceding claim wherein
10 said chelating agent residue is of a chelating agent selected from the group consisting of EDTA, DTPA, DOTA, DO3A, OTTA, CDTPA, P4A, B4A, PheMT, DCDTPA and TMT.

8. A polymer as claimed in claim 4 wherein R"
15 represents hydrogen or an alkylene group optionally interrupted by one or more heteroatoms.

9. A polymer as claimed in claim 4 wherein L
independently represents carbon, amino, imido, nitrilo,
imino, alkylene, carbonyl, sulfonyl, sulfinyl, ether,
20 thioether, ester, thioester, amide, thioamide, thio, dithio, phosphate, phosphonate, urelene, thiourelene, urethane, thiourethane, an amino acid linkage or a peptide linkage.

25 10. A polymer as claimed in claim 4 wherein L independently represents an imino or nitrilo linkage.

11. A polymer as claimed in claim 4 wherein said group
30 PAO- is selected from the group consisting of a poly(ethylene oxide) moiety, a poly(propylene oxide) moiety and a poly(ethylene oxide)-copoly(propylene oxide) moiety.

12. A polymer as claimed in claim 4 wherein -OR is
35 selected from the group consisting of OH, OCH_3 , $O(CH_2)_pCH_3$ where $p = 2$ to 20.

- 40 -

13. A polymer as claimed in any preceding claim comprising from 2 to 1000 of said polymeric units.

14. A polymer as claimed in any preceding claim
5 comprising from 5 to 100 of said polymeric units.

15. A polymer as claimed in claim 4 wherein said metal is Gd^{3+} or Dy^{3+} ; L and R" together are $N(CH_2CH_2NH_2)_3$ or $H_2NCH_2CH_2(OCH_2CH_2)_2NH_2$; R is CH_3 ; R' is H or -PAO-OR; PAO
10 is a poly(ethylene oxide) moiety of MW 200-20,000; and said chelator is DTPA.

16. A polymer as claimed in claim 4 wherein said metal is Gd^{3+} ; L and R" together are $N(CH_2CH_2NH_2)_3$; R is CH_3 ; R'
15 is H; PAO is a poly(ethylene oxide) moiety of MW 550; and said chelator is DTPA.

17. A pharmaceutical composition comprising a polymer as claimed in any of claims 1 to 16 together with one or
20 more pharmaceutically acceptable carriers or excipients.

18. A method of generating an enhanced MR image of the human or non-human animal body, said method comprising administering to said body a contrast enhancing amount
25 of a paramagnetic metal containing polymer as claimed in any of claims 3 to 16 and generating an MR image of at least a part of said body into which said polymer distributes.

19. A process for the preparation of a polymer as claimed in claim 1, said process comprising one or more
30 of the following steps:

(a) reacting a poly(alkylene oxide) or a derivative thereof with a chelating agent or precursor
35 therefor containing reactive functionality;

(b) a condensation polymerisation reaction between a polyamine and a diacid containing the metallised

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chelating group or an activated derivative thereof;

(c) protecting the reagents of either of steps (a) or (b) with suitable protecting groups and subsequently removing said protecting groups.

5

20. A process as claimed in claim 19 comprising reacting a linear α -(polyamino)-poly(alkylene oxide) with a chelating agent or precursor therefor in an internal dianhydride form.

10

21. Use of a polymer as claimed in claim 1 for the manufacture of diagnostic or therapeutic agents for use in a method of image generation or therapy practised on the human or non-human animal body.

15

22. Use of a radioactive metal species containing polymer as claimed in any of claims 3 to 16 in radiotherapy.

20

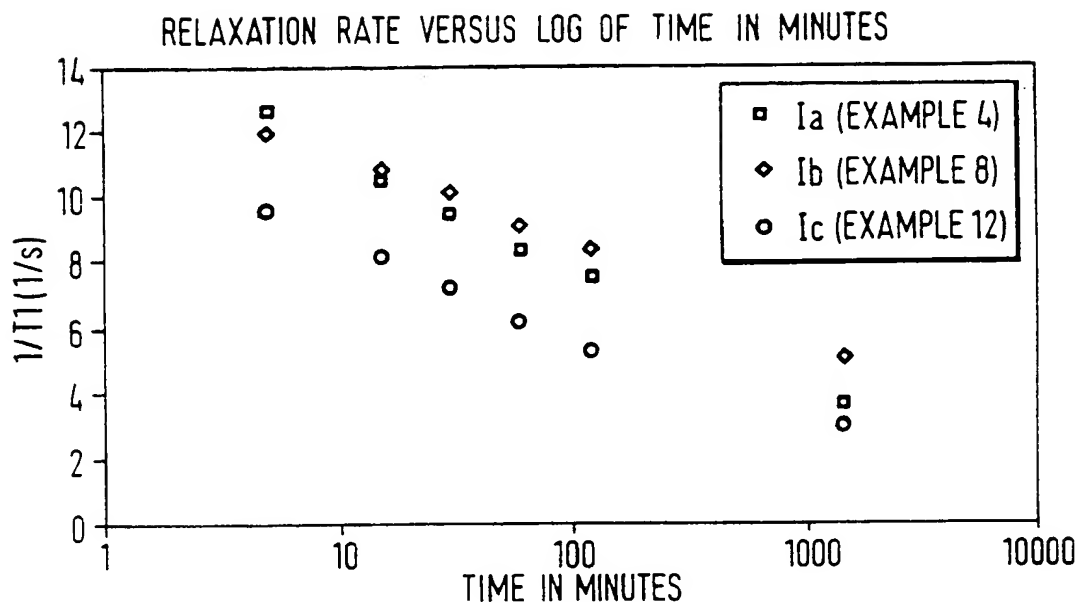
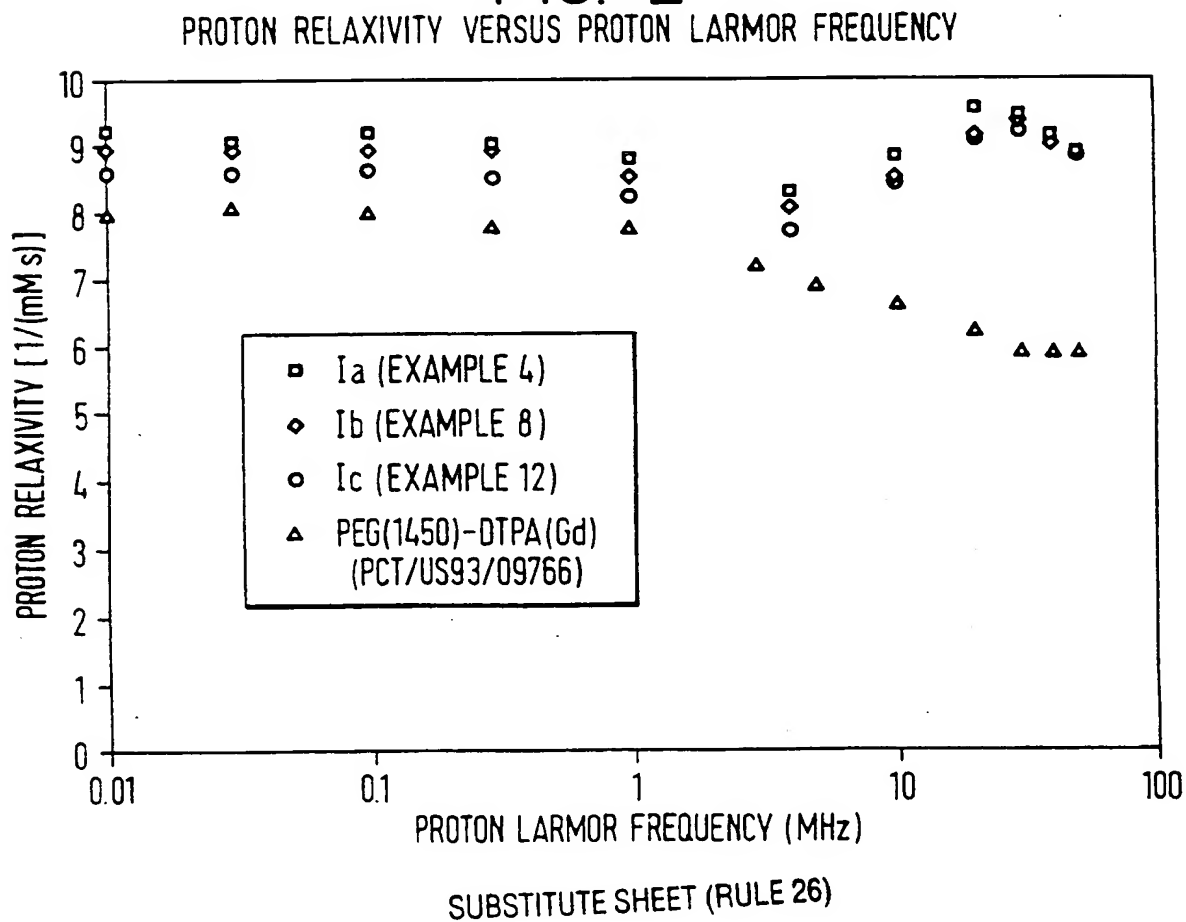
1 / 2
FIG. 1

FIG. 2



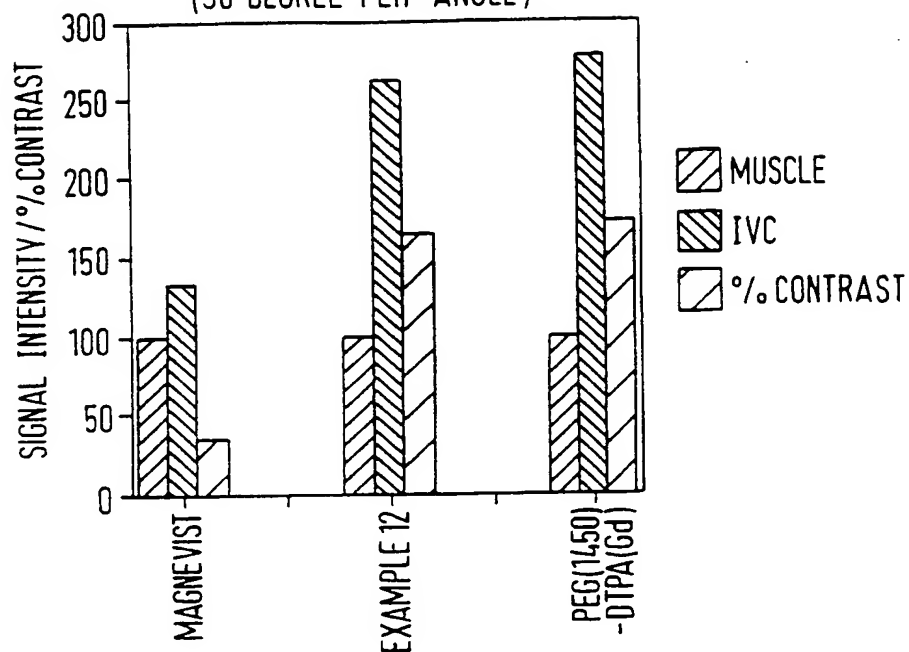
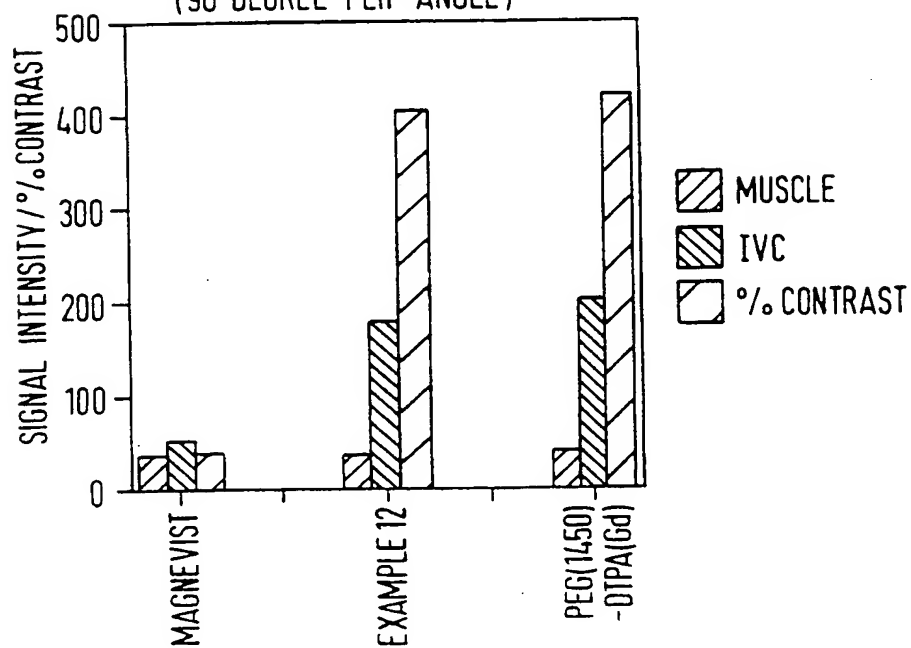
2 / 2
FIG. 3IVC vs. MUSCLE: FIVE MINUTES
(30 DEGREE FLIP ANGLE)

FIG. 4

IVC vs. MUSCLE: 15 MINUTES
(90 DEGREE FLIP ANGLE)

SUBSTITUTE SHEET (RULE 26)

INTERNATIONAL SEARCH REPORT

Inter. Application No

/GB 95/01514

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K49/00 A61K51/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 08629 (STERLING WINTHROP INC) 28 April 1994 cited in the application see claims 1,3-6,8; examples ---	1-22
P,X	WO,A,94 28940 (GEN HOSPITAL CORP) 22 December 1994 see claims 1,6,7,9-12 ---	1-22
A	EP,A,0 233 619 (NIHON MEDIPHYSICS CO LTD) 26 August 1987 see claims; examples ---	
X	WO,A,94 05203 (GEN HOSPITAL CORP) 17 March 1994 see page 8, line 1 - page 9, line 34 see page 19, line 4 - line 13 see page 23, line 7 - line 16; example 1 --- -/--	1-22

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- * & * document member of the same patent family

Date of the actual completion of the international search

11 October 1995

Date of mailing of the international search report

27. 10. 95

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO,A,92 00748 (ENZON INC) 23 January 1992 see claims -----	1-22

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Inter. Application No

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